

5-Fluorouracil in the treatment of penile and urethral condylomata acuminata

JOHAN WALLIN

From the Department of Dermatology and Venereology, University Hospital, Uppsala, Sweden

SUMMARY 5-Fluorouracil (5-FU) cream was compared with podophyllin 25% in alcohol for treating genital and urethral condylomata acuminata. The cure rate after four weeks was found to be 6 of 18 patients treated with 5-FU and 10 of 19 treated with podophyllin. By changing the treatment for those not cured, warts regressed after four weeks in four more patients in each group. Patients were followed-up for four to nine months; 10 of 27 treated with 5-FU and 14 of 31 treated with podophyllin remained in remission. It is not possible to support earlier reports on the successful treatment of meatal warts using 5-FU cream. More than half of the patients given 5-FU reported side effects after 10 to 14 days' treatment, which in some cases led them to stop using the cream. Twenty-one men considered to be treatment failures or relapses were examined by urethroscopy. No intraurethral condylomata were found but three cases of warts in the fossa navicularis were discovered; this prompted us to introduce an instrument to examine the urethral meatus and the fossa navicularis.

Introduction

The incidence of condylomata acuminata in England and Wales during 1974 was about one-third of that of gonorrhoea in both sexes (Willcox, in press). At the Department of Venereal Diseases, University Hospital, Uppsala, Sweden, genital warts were diagnosed in 7.8% of male patients (Wallin, 1975).

Various methods of treatment are used, and among those favoured is a local application of a 25% solution of podophyllin dissolved in alcohol. However, the treatment failures with this method, especially among patients with meatal warts, constitute a considerable problem (Halverstadt and Parry, 1969; Gigax and Robison, 1971). Some of these failures may be explained by condylomata situated within the urethra, which can easily be overlooked. So far nothing has been published on the occurrence of intraurethral condylomata in men with genital warts.

The purpose of this study was to compare the effect and tolerance of a 5% 5-fluorouracil (5-FU) cream with a 25% podophyllin solution for the topical treatment of condylomata acuminata in men. A further aim was to study the occurrence of intra-

urethral warts in those men who were regarded as treatment failures.

Patients and methods

All male patients with condylomata acuminata who attended the clinic between September 1975 and January 1976 were included except patients who had been treated during the previous six months for genital warts, and those unable to return for follow-up visits. The patients studied comprised 42 men whose ages ranged between 19 and 36 years (mean 24). Duration, appearance, and distribution of the genital warts were recorded in all patients. The terms hyperplastic, sessile, and verruca vulgaris were used to define the appearance as described by Oriel (1971). Warts situated in the meatus were studied separately.

The patients were allocated two treatment groups using a table of random numbers. The two groups of patients were comparable in terms of age, country of birth, marital state, and size and distribution of their warts.

GROUP 1

Twenty patients were told to apply 5-FU cream with cotton swabs every evening for a period of two weeks. The effect was studied after one, two, and four weeks. If side effects were experienced

Address for reprints: J. Wallin, Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Atlanta, Georgia 30333, USA

Received for publication 21 February 1977

the patients were instructed to stop treatment and keep the lesions clean with soap and water until the next visit to the clinic.

GROUP 2

Twenty-two patients received treatment with a 25% podophyllin solution, which was applied to the warts by the doctor once a week for four consecutive weeks. The solution was washed off with soap and water after four to six hours. The effect was evaluated in the clinic each week and one week after the final application.

All patients were strongly advised to refrain from sexual intercourse during the month of treatment and observation and told to use a condom during the follow-up period. The patients who still had genital warts at the end of the four weeks were referred to a urologist and a urethroscopical examination was made during the fifth week of the study. The entire urethra was then carefully inspected. Patients with intraurethral condylomata were instructed to instil 5-FU cream into the meatus once every day for two weeks, as described by Dretler and Klein (1975). When urethroscopy gave normal findings the patient was changed to the other treatment schedule. The patients who were regarded as having been cured were observed during a follow-up period which lasted between four and nine months.

Treatment failure was defined as total absence of response to treatment. Relapse was defined as initial resolution but reappearance of warts during the period of follow-up. The χ^2 test of significance was applied to the results of treatment.

Results

Two patients in group 1 and three in group 2 failed to return for a sufficient number of examinations, and were therefore excluded from the study. Most of the remaining 37 patients (67.6%) had had their warts for less than six months. The hyperplastic type of warts was found in 29 cases (78.5%), the sessile type in 17 (46.0%), and the verruca vulgaris-type in three (8.1%). The distribution of the condylomata is presented in Table 1.

Table 1 *Distribution of genital warts*

Site	Percentage of patients affected
Fraenum, corona, and glans	70
Prepuce (all parts)	49
Urinary meatus	24
Shaft of penis	16
Scrotum	0
Anus	3

TREATMENT

No significant difference regarding the results of the two treatments could be found between the groups (Tables 2 and 3). None of the men with meatal warts was cured by podophyllin treatment, which meant that each was started on the 5-FU schedule. In all, nine patients with meatal warts had two weeks' treatment with 5-FU, but total regression was seen in only one patient. Intraurethral applications of 5-FU were also tried during another two weeks in three cases with multiple masses of warts in the fossa navicularis. One man was completely cured, while no clinical change was observed in the other two.

In the men with negative urethroscopical findings the treatment regimen was changed from 5-FU to podophyllin and vice versa. Table 4 shows that another eight patients were cured, four were given 5-FU, and four were given podophyllin. The total cure rate for 5-FU was 10 of 27 (37.0%) and for podophyllin it was 14 of 31 (45.3%). Altogether 24 men out of 37 treated had a total regression of their genital warts.

Table 2 *Effect of four weeks' treatment on hyperplastic, sessile, and meatal warts*

Type	Treatment	
	5-FU	Podophyllin
Hyperplastic	7/14	11/15
Sessile	6/8	6/9
Meatal	1/3	0/6
No. of patients	18	19

Table 3 *No. of patients recorded as cured after four weeks and at the final visit after 4 to 9 months (mean 5.8)*

Period	Treatment	
	5-FU	Podophyllin
4 weeks	10/18	11/19
Final visit	6/18	10/19

Table 4 *The effect of first treatment and cross-over treatment*

Cured	Treatment	
	5-FU	Podophyllin
By the first treatment	6/18	10/19
After cross-over treatment	4/9	4/12
No. cured	10/27	14/31
Percentage cured	37.0	45.3

TOLERANCE

Podophyllin was very well tolerated and only one patient complained of small erosions on the glans after the third application. Treatment with 5-FU caused erythema and itching shortly afterwards, followed by superficial painful ulcerations. Such side effects, which appeared 6–12 days (mean 10 days) after the treatment had started, were reported by 55% in group 1. Four of the patients who experienced side effects had to stop the treatment for two or three days and then continued with it to complete the period of two weeks.

URETHROSCOPICAL EXAMINATION

During the study urethroscopy was performed in 21 men; 16 were considered to be treatment failures and five were relapses. Intraurethral condylomata were not found in any of these patients. Three out of eight men with meatal warts were found to have multiple masses in the fossa navicularis, which had not been discovered at the clinical routine examination. Strictures were seen in three patients (14.2%); all of them had a history of gonorrhoea. In all such a history was found for five of the men in the study.

Discussion

At the Venereal Diseases Clinic in Uppsala podophyllin is the most commonly used treatment in the management of genital warts. In many cases a small amount of a 25% podophyllin solution, applied to the wart for several hours, is effective. However, as reported by von Krogh (1976) the results have been discouraging during the past years for unknown reasons. A total regression of the warts after podophyllin was reported in 20% of the men (von Krogh, 1976). Podophyllin acts on normal skin and mucous membranes and the disadvantage of this treatment is the possible development of painful oedema with local ulcerations. In addition, to reduce the side effects patients have to visit the clinic once a week to have the drug applied instead of treating themselves at home. This makes long-term treatment with podophyllin inconvenient and time consuming for the patients and the doctor. An alternative treatment of condylomata acuminata, which has been tried is 5-FU (Binazzi, 1970; Dretler and Klein, 1975; von Krogh, 1976).

The two treatments gave the same results which were unrelated to distribution, type, and appearance of the warts. After four weeks of treatment 56.7% of the patients were cured. By giving those patients who failed to respond to one drug the other for another period of two or four weeks, a total regression was seen in 64.9% after a follow-up of four to nine months. After four applications, 58% of those

treated with podophyllin were considered to be cured, which is quite close to the 64% treated and followed-up in the same way by von Krogh (1975).

Side effects after podophyllin treatment were reported by only one patient in this study, while the side effects of the daily 5-FU treatment were a problem for more than half of the patients within 10 to 14 days, although they were told to be cautious when applying the cream. As these patients developed painful ulcers on the sites of the application, the 5-FU treatment had to be stopped and some patients refused to resume treatment. In some cases, in which the warts persisted or had recurred, a combination of four podophyllin applications followed by 10 to 14 days' use of 5-FU cream was recommended in order to obtain the best possible effect with a minimum of side effects.

The current study does not support the encouraging results of 5-FU in the treatment of meatal condylomata acuminata reported by Dretler and Klein (1975) and von Krogh (1976). These authors found that 15 of 15 men treated daily for between three and eight days were cured as were 13 of 14 men treated for 2.5 to 9.3 weeks (mean 3.4 weeks). Among those treated in the current study only one out of nine men with meatal warts was cured by the use of 5-FU during a period, limited by the side effects, of about two weeks. However, the number of patients in all these three studies is too small to compare. Most of our patients had had their warts for less than six months compared with those treated by von Krogh, for whom the average duration was about one year. Dretler and Klein (1975), as well as von Krogh (1976), have not clearly stated how many of the men initially included failed to attend the follow-up examinations.

Surprisingly few studies have been made regarding the presence of intraurethral condylomata. These apparently rarely involve the urethra, but no figures are available on the incidence. In fact no study has been published where the urethra has been endoscopically examined in patients suffering from genital warts.

As a result of the observation of warts in the fossa navicularis we have introduced the use of a speculum for the examination of the fossa. This type of instrument is normally used by the otolaryngologists to examine the mucous membranes of nostrils.

References

- Binazzi, M. (1970). Clinical and structural evaluation of the treatment of some hyperplastic and neoplastic skin diseases with 5-fluorouracil (5-FU) ointment. *Dermatologica*, 140, Supplement I, 90–96.
- Dretler, S. P., and Klein, L. A. (1975). The eradication of intra urethral condyloma acuminata with 5 per cent 5-fluorouracil cream. *Journal of Urology*, 113, 195–198.

- Gigax, J. H., and Robison, J. R. (1971). The successful treatment of intraurethral condyloma acuminata with colchicine. *Journal of Urology*, 105, 809-811.
- Halverstadt, D. B., and Parry, W. L. (1969). Thiotepa in the management of intraurethral condylomata acuminata. *Journal of Urology*, 101, 729-731.
- Oriel, J. D. (1971). Natural history of genital warts. *British Journal of Venereal Diseases*, 47, 1-13.
- von Krogh, G. (1975). Lokalisation, spridningssätt och behandling av condylomata acuminata. *Läkartidningen (Stockholm)*, 72, 2167-2170.
- von Krogh, G. (1976). 5-fluorouracil cream in the successful treatment of therapeutically refractory condylomata acuminata of the urinary meatus. *Acta dermato-venereologica*, 56, 297-301.
- Wallin, J. (1975). Gonorrhoea in 1972. A 1-year study of patients attending the VD unit in Uppsala. *British Journal of Venereal Diseases*, 51, 41-47.
- Willcox, R. R. Extent and trends of the sexually transmitted diseases in the European region of WHO. III. Those of other than syphilis and gonorrhoea. *Vienna Symposium 1976*. WHO Regional Office: Copenhagen. In press.